



# Anaphylaxis in dogs and cats

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## Abstract

**Objective** – To review and summarize current information regarding the pathophysiology and clinical manifestations associated with anaphylaxis in dogs and cats. The etiology, diagnosis, treatment, and prognosis is discussed.

**Etiology** – Anaphylaxis is a systemic, type I hypersensitivity reaction that often has fatal consequences. Many of the principal clinical manifestations involve organs where mast cell concentrations are highest: the skin, the lungs, and the gastrointestinal tract. Histamine and other deleterious inflammatory mediators promote vascular permeability and smooth muscle contraction; they are readily released from sensitized mast cells and basophils challenged with antigen. Anaphylaxis may be triggered by a variety of antigens including insect and reptile venom, a variety of drugs, vaccines, and food.

**Diagnosis** – Anaphylaxis is a clinical diagnosis made from a collection of signs and symptoms. It is most commonly based on pattern recognition. Differential diagnoses include severe asthma, pheocromocytoma, and mastocytosis.

**Therapy** – Epinephrine is considered the drug of choice for the treatment of anaphylaxis. It acts primarily as a vasopressor in improving hemodynamic recovery. Adjunctive treatments include fluid therapy, H<sub>1</sub> and H<sub>2</sub> antihistamines, corticosteroids, and bronchodilators; however, these do not substitute for epinephrine.

**Prognosis** – Prognosis depends on the severity of the clinical signs. The clinical signs will vary among species and route of exposure. The most severe clinical reactions are associated when the antigen is administered parenterally.

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## Introduction

Definitions for anaphylaxis in common use include “a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy causing substance”<sup>1</sup> and “a serious allergic reaction that is rapid in onset and might cause death.”<sup>2</sup> From the standpoint of the specialist in allergy-immunology, an anaphylactic reaction is mechanistically defined as “a systemic, immediate hypersensitivity reaction most commonly caused by IgE-mediated immunologic release of mediators from mast cells and basophils.”<sup>3</sup> The term, *anaphylaxis*, is derived from the Greek words *a* (against) and *phylaxis* (protection). The phenomenon of anaphylaxis was first described in 1902 by Portier and Richet when they were attempting to produce tolerance in dogs to sea anemone

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## Abbreviations

ALT	Alanine transaminase
AVP	Arginine-vasopressin
CO	Cardiac output
H1R	H1 histamine receptor
H2R	H2 histamine receptor
H3R	H3 histamine receptor
H4R	H4 histamine receptor
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
MAP	Mean arterial pressure
NO	Nitric oxide
NSAIDs	Nonsteroidal anti-inflammatory agents
PAF	Platelet activating factor
SRS-A	Slow-reacting substances of anaphylaxis
VAAEs	Vaccine-associated adverse events
WAO	World Allergy Organization

venom. Rather than generating protection, it precipitated the rapid onset of fatal or near-fatal symptoms. They

concluded that the immune system first becomes sensitized to the allergen over several weeks and upon re-exposure to the same allergen may result in a severe reaction. They coined the term "aphylaxis" to differentiate it from the expected "prophylaxis" they hoped to achieve. The term *aphylaxis* was replaced with the term *anaphylaxis* shortly thereafter.<sup>3,4</sup>

Although anaphylaxis was first described over 100 years ago and is one of the most alarming disorders encountered in humane medicine, the definition of this term has been elusive since its discovery and there is still debate as to the proper definition for the term "anaphylaxis." It seems anti-intuitive that a phenomenon with such explosive manifestations and distinct symptoms should be difficult to define. The lack of specific criteria for diagnosing anaphylaxis has greatly hampered research into the epidemiology, pathophysiology, and management of this disorder, subsequently resulting in a failure to diagnose and treat anaphylaxis in a consistent manner.<sup>1</sup> In the last decade, great effort has been made to determine the criteria necessary to make a diagnosis and to establish appropriate terminology suitable for all episodes.<sup>3</sup> Published reports of anaphylactic reactions in veterinary patients are unusually rare.<sup>5</sup> To the authors' knowledge, there are less than 25 clinical reports published since 1950, most of which described reactions to antimicrobials, vaccines, and Hymenoptera stings.<sup>6–25</sup> This makes determining the risks of anaphylaxis difficult to assess in veterinary patients, as it is likely that many more reactions have been observed, but go unreported for a variety of reasons. This review relies on both the human and veterinary literature to summarize the pathophysiology, clinical presentation, therapeutic recommendations, and prognosis of anaphylaxis.

### Epidemiology

Only 1% of human emergency department visits for acute systemic allergic reactions receive the diagnosis of anaphylaxis; many visits are coded as "acute allergic reactions," or "acute hypersensitivity reactions."<sup>26</sup> There is consistent failure to appreciate the variable presentations and disagreement among physicians in what is severe enough to be considered anaphylaxis rather than an allergic reaction.<sup>1,27</sup> Underreporting and miscoding of anaphylaxis remain current important issues in human as well as in veterinary medicine. In prospective human medicine studies, underreporting likely occurs because anaphylaxis may be underdiagnosed in individuals who present with mild or partially treated episodes.<sup>26</sup> Also, underdiagnosing is more likely to occur if it is a patient's first episode or if there is a hidden or previously unrecognized trigger.<sup>26,28</sup> A recent review of the available

epidemiologic evidence in human medicine estimated that the frequency of anaphylaxis was approximately 50–2,000 episodes per 100,000 persons or a lifetime prevalence of 0.05–2.0%.<sup>2,26,29–31</sup>

Although the prevalence of anaphylaxis in small animals is unknown, anaphylactic reactions are being seen with increasing frequency, as the number of antigenic substances to which patients are exposed increases, both as diagnostic aids and therapeutic modalities.<sup>5</sup> Moreover, nearly any foreign substance by any route of exposure is a potential cause of these reactions.<sup>28</sup> The sudden, often unanticipated, onset and the catastrophic impact of anaphylaxis makes proper diagnosis and appropriate treatment critical to favorable patient outcomes.

### Pathophysiology

Anaphylaxis is a systemic, immediate type hypersensitivity reaction.<sup>28,31</sup> The traditional nomenclature for anaphylaxis reserves the term *anaphylactic* for reactions mediated by immunoglobulin E (IgE) and the term *anaphylactoid* for IgE-independent events. Clinically, these are indistinguishable; therefore, diagnosis and treatment are identical. In 2003, the World Allergy Organization (WAO) suggested that the term "anaphylactoid" be abandoned and all such events, regardless of the mechanism of production, be called "anaphylactic episodes."<sup>2</sup> The WAO further suggested that these anaphylactic episodes be divided into immunologic and nonimmunologic events.<sup>2</sup> The nonimmunologic anaphylactic events could be considered synonymous with the term "anaphylactoid," and the immunologic events were further subcategorized as IgE- and non-IgE-mediated.<sup>2</sup> The debate as to whether all clinically similar events, not mediated by IgE, should also be referred to as *anaphylactic* as suggested by the WAO or called *anaphylactoid* reactions still rages on.

Anaphylactic reactions are currently classified as follows:<sup>2,31</sup>

1. Immunologic IgE-mediated: Causes include, but are not limited to, insect stings/bites, reptile venom, food, and medications (eg,  $\beta$ -lactam antimicrobials).
2. Immunologic non-IgE-mediated: Caused, for example, by immune aggregates (eg, IV immunoglobulin, such as IgG- or IgM-related, transfusion), complement system activation, coagulation system activation, and autoimmune mechanisms.
3. Non-immunologic: Causes include, but are not limited to, physical factors (eg, cold, water exposure, heat, and exercise), certain medications (eg, opioids), and some chemotherapeutic agents.

### Immunologic anaphylaxis

The pathogenesis of anaphylaxis is fairly obscure and its complexity can adversely impact clinical management. Studies in murine models have identified 2 distinct immunologic pathways of systemic anaphylaxis. The first is the classic IgE-mediated hypersensitivity reaction.<sup>32–36</sup> IgE antibodies are produced in response to an initial exposure to an antigen and bind to high-affinity IgE receptor known as FcεRI, located in the plasma membrane of tissue mast cells and blood basophils.<sup>4,37–40</sup> The antigen to which one produces an IgE antibody response that leads to an allergic reaction is called an allergen, which has a molecular weight between 10 and 40 kDa.<sup>41</sup> IgE is typically found in very low concentrations in serum because of its low production, short half-life (approximately 2 days), and sequestration on mast cells and basophils.<sup>41</sup> The IgE antibodies produced in serum may recognize various epitopes of the allergen. Once recognized, the antibodies bind to mast cells and basophils allowing them to participate in the immediate hypersensitivity reaction upon appropriate antigenic stimulation. This initial phase of sensitization is clinically silent. Upon reexposure, the multimeric allergen forms a bridge across the 2 cell-bound IgE antibody molecules and cross-links them.<sup>26,33,38–40</sup> The cross-linking induces a membrane change that leads to an influx of calcium ions and changes in cyclic nucleotide levels, which in turn triggers the release of various pharmacologically active substances. This series of reactions results in the generation and rapid release of preformed mediators, such as histamine, stored in the mast cell granules, as well as production of newly formed mediators, such as platelet activating factor (PAF) and upregulation of cytokine synthesis.<sup>4,26,33,39,40</sup> The interaction of these mediators with host target organ systems results in the clinical manifestations of anaphylaxis.<sup>28,32–36</sup>

The second, alternative, pathway of anaphylaxis is IgE-independent. This pathway has not been confirmed in people. In contrast to the classic allergic reaction, this alternative pathway is mediated by immunoglobulin G (IgG), FcγRIII receptors, and macrophages. It requires proportionately more antigen and antibody than the first pathway. Systemic anaphylaxis is induced by antigen binding to IgG molecules that cross-link the low-affinity receptors for IgG (FcγRIII) on macrophages.<sup>36</sup> While both mechanisms release PAF, only the IgE-dependent mechanism releases histamine.<sup>32–34,36,42</sup> Murine studies have also demonstrated that IgG antibodies can block IgE-dependent anaphylaxis under conditions of high IgG antibody concentration and low allergen dose without causing anaphylaxis through the alternative pathway.<sup>34,43</sup> A recent research study investigated the role of neutrophils in anaphylaxis. It was concluded that mouse and human neutrophils each restored anaphy-

laxis in anaphylaxis-resistant mice, demonstrating that neutrophils are sufficient to induce IgG-dependent anaphylactic reactions in mice and thus, suggesting that neutrophils may contribute to anaphylaxis in people.<sup>44</sup>

The precise mechanism as to why some animals are more prone to type-I hypersensitivity is not clear. However, it has been shown that such animals preferentially produce more of the lymphocyte subtype CD4<sup>+</sup> T-helper 2 cells. These specific cells are central in the induction of the IgE antibody response.<sup>4</sup> Activation of CD4<sup>+</sup> T-helper 2 cells also leads to production of interleukin (IL)-4 and IL-13, which direct B-cell differentiation into IgE secreting plasma cells.<sup>4,33</sup>

### Nonimmunologic anaphylaxis

Nonimmunologic anaphylaxis occurs when agents cause degranulation of mast cells and basophils without help from immunoglobulins. Examples include: physical factors (eg, heat, cold, exercise), drugs, such as nonsteroidal anti-inflammatory agents (NSAIDs) and opioids, ethanol and radiocontrast agents.<sup>31,33,45–47</sup> Some triggers, such as radiocontrast agents and medications (eg, NSAIDs), potentially act through more than one mechanism.<sup>3,31,47</sup> In some cases, no trigger is identified and is considered as idiopathic anaphylaxis.<sup>29,42</sup>

### Chemical Mediators of Anaphylaxis

While histamine remains the principal mediator in anaphylaxis, a range of other mediators have been implicated in human studies, in vitro cell stimulation studies, and animal models.<sup>48</sup> The preformed mediators stored in the granules of mast cells and basophils that prompt degranulation and immediate release include histamine, heparin, proteases, such as, tryptase, chymase, carboxypeptidase A3, and proteoglycans. Downstream activation of phospholipase A2, followed by cyclooxygenases and lipoxygenases, produces newly synthesized proinflammatory chemical mediators. These mediators, principally derived from the arachidonic acid metabolites, include prostaglandin D2, leukotriene B4 (LTB4), cystenyl leukotrienes (LTC4, LTD4, LTE4), and PAF.<sup>4,15,33,43,44,46,49</sup> In addition, a multitude of cytokines and chemokines are synthesized and released including IL-4, IL-5, IL-6, IL-8, IL-9, IL-13, newly recognized IL-33,<sup>50</sup> and tumor necrosis factor-α.<sup>51</sup> The latter cytokine is both a preformed and a late-phase mediator.<sup>44,51</sup> Consequently, shock develops as a result of rapid release of potent inflammatory and vasoactive mediators. This in turn leads to increased vascular permeability, hypovolemia, and vasodilation. Moreover, these chemical mediators may also directly impair cardiac function, which may further exacerbate the effects of circulatory abnormalities.<sup>33,46</sup>

Anaphylaxis also depends on cellular responsiveness to the released mediators. IL-4 and IL-13 are important cytokines in the initial generation of antibody and inflammatory cell responses to anaphylaxis.<sup>33</sup> The most rapid, dramatic effect of IL-4 in murine anaphylaxis is a 3- to 6-fold increase in cellular responsiveness to inflammatory and vasoactive mediators, including histamine, leukotrienes, and PAF.<sup>34</sup> In mice, increased IL-4 receptor signaling also enhances risk of anaphylaxis.<sup>52</sup>

Other concomitant pathways activated during anaphylaxis include the complement system, the kallikrein-kinin contact system, the coagulation cascade, and the fibrinolytic system.<sup>4,43,53-55</sup> Activation of the complement system with generation of C3a has been observed in anaphylaxis.<sup>3,43</sup> C3a, an anaphylatoxin, leads to basophil and mast cells degranulation, enhanced vascular permeability, and smooth muscle contraction.<sup>43</sup> The activation of kallikrein not only results in the formation of bradykinin, a powerful vasodilator, but also activation of factor XII. Factor XII contributes to clot formation, and also clot lysis through plasmin formation. Plasmin can also activate complement.<sup>43</sup> Demonstrable evidence for coagulation pathway alteration includes decreases in factor V, factor VIII, fibrinogen, and disseminated intravascular coagulation.<sup>43,53</sup>

Severe and fatal anaphylactic events can be related not only to the amount of mediators released, but also to the rapidity of their degradation.<sup>56</sup> This systemic response progresses rapidly with the release of mediators within seconds to minutes, the arachidonic cascade is activated within 5–30 minutes, while cytokine synthesis is activated within 2–6 hours.<sup>4,41,43,55,57</sup> These overlapping and synergistic physiological effects contribute to the overall pathophysiology that results in the clinical findings of cardiovascular collapse, respiratory compromise, and circulatory shock observed with anaphylaxis. In contrast, some mediators may have anti-inflammatory and modulatory effects that limit anaphylaxis.<sup>33</sup> Heparin modulates tryptase activity, opposes complement, and inhibits clot formation, plasmin, and kallikrein.<sup>33,53</sup> Chymase stimulates the conversion of angiotensin I into angiotensin II, independent of angiotensin converting enzyme, and may potentially help to decrease the severity of hypotension.<sup>33,54</sup> One study on rat mast cells revealed that the net release of these two mediators (eg, heparin and chymase) was much less than that of histamine, and net release of heparin was detected only when the net percent release of histamine was >10% in rat mast cells.<sup>58</sup> This study revealed that chymase and heparin proteoglycan were released but were retained at the cell surface in a relatively insoluble complex. This, in turn, permitted quantitation of the amount of chymase and heparin present in secretory granules.<sup>58</sup>

## Histamine

Histamine is synthesized by mast cells, basophils, platelets, histaminergic neurons, and enterochromaffin cells where it is stored intracellularly in vesicles and released upon stimulation.<sup>59</sup> Mast cells and basophils are the major sources of histamine in normal tissue, comprising up to 70% of the weight of each cell.<sup>59-61</sup> Histamine release is rapid and measurable concentrations are found in plasma within 1 minute of an anaphylactic episode.<sup>59,61</sup> The diverse effects of histamine are mediated through different histaminergic receptors. Histamine acts through receptors H1, H2, and H3 to promote circulatory shock during allergen challenge.<sup>43,59,62,63</sup> H1 histamine receptor (H1R) activities include smooth muscle contraction and interaction with the endothelium, leading to vasodilatation and increased vascular permeability. This in turn results in rhinitis, pruritus, bronchoconstriction, coronary vasoconstriction, and cardiac depression.<sup>59</sup> H1R also stimulates endothelial cells to convert the amino acid L-arginine into nitric oxide (NO), a potent autocoid vasodilator.<sup>43,59,64</sup> Enhanced NO production decreases venous return, thus contributing to the vasodilation that occurs during anaphylaxis.<sup>43</sup> H2 histamine receptor (H2R) stimulates gastric acid secretion, produces coronary and systemic vasodilation, increases in heart rate, and ventricular contractility. H3 histamine receptors (H3R) have recently been identified on presynaptic terminals of sympathetic effector nerves that innervate the heart and systemic vasculature.<sup>43,57,59,62,65</sup> These receptors have been found to inhibit endogenous norepinephrine release from the sympathetic nerves. H3R activation would therefore be expected to accentuate the degree of shock observed during antigen challenge since compensatory neural adrenergic stimulation would be prevented. Moreover, murine models suggest H4 receptors (H4R) might be involved in chemotaxis and mast cell cytokine release and may also help to mediate pruritus.<sup>33,66</sup>

## Prostaglandins, leukotrienes, and other mediators

Prostaglandin D<sub>2</sub>, a cyclooxygenase pathway product, acts as a bronchoconstrictor, pulmonary and coronary vasoconstrictor, and peripheral vasodilator.<sup>32,44</sup> Alternatively, the lipoxygenase pathway yields mainly systemic vasoconstrictors that are the active constituents of the slow-reacting substances of anaphylaxis (SRS-A). Compared to histamine, the SRS-A is approximately 1,000-fold more potent and has a slower onset but longer duration of action.<sup>28</sup> LTC<sub>4</sub> is converted into LTD<sub>4</sub> and LTE<sub>4</sub> and increases bronchoconstriction, vascular permeability, and promotes airway remodeling.<sup>4,32,44,67</sup> LTB<sub>4</sub> is a chemotactic agent and theoretically might contribute to the late phase of anaphylaxis and to

protracted reactions.<sup>43</sup> Of the newly formed mediators, PAF, a potent bronchoconstrictor, has been suggested to play a major role in anaphylaxis. PAF decreases coronary blood flow and myocardial contractility, causes a prolonged increase in pulmonary resistance, and induces local and systemic platelet aggregation as well as peripheral vasodilatation and severe hypotension.<sup>32,46,49,67,68</sup> Tumor necrosis factor- $\alpha$  activates neutrophils, recruits other effector cells, and increases chemokine synthesis.<sup>32</sup> Tryptase, a serine protease activates complement, coagulation pathways, and the kallikrein-kinin contact system with the potential clinical consequences of hypotension, angioedema, clot formation, and disseminated intravascular coagulation.<sup>33,46</sup>

### Shock Organs

There are well-recognized species differences for acute systemic anaphylaxis in the major organ systems affected and the associated clinical signs. The different physiological response to a similar antigen challenge is influenced by variations in immune response, location and distribution of smooth muscle, rate of antigen degradation, and responsiveness to inflammatory mediators.<sup>33</sup> Clinical manifestations of anaphylactic reactions are therefore species dependent and directly related to the location of the largest population of mast cells.<sup>73</sup> In people, the predominant "shock organs" are the lungs and the heart.<sup>33,43,69</sup> In the dog, the gastrointestinal tract and the liver<sup>57,70-73</sup> are the primary affected organs, whereas in the cat the respiratory tract predominates.<sup>57,69-71,73-75</sup>

In dogs, it appears that the severity of shock is directly proportional to the degree of congestion to the liver and gallbladder.<sup>77</sup> Histamine is released from the gastrointestinal tract into the portal vein during anaphylaxis; this causes hepatic arterial vasodilation and a concurrent increase in arterial hepatic blood flow within seconds.<sup>73,78</sup> The intraportal infusion of histamine also causes a considerable increase in hepatic venous outflow obstruction (attributed to the hepatic venous sphincter at the junction of the inferior vena cava and the hepatic veins in the dog) which, in turn, increases the hepatic portal vascular resistance significantly (up to 220% in approximately 12 seconds).<sup>73,78,79</sup> Consequently, the portal blood supply and the venous return from the liver to the systemic circulation are severely compromised.<sup>73,78-80</sup> Since the cardiac output (CO) is generally equal to that of venous return, it is the reduced venous return rather than a failing heart that accounts for the markedly suppressed CO observed.<sup>81</sup> This said, histamine acts primarily on hepatic veins to raise intrahepatic pressure and produce massive infiltration of fluid, which results in an insuf-

ficient return of blood to the heart.<sup>78</sup> Hepatic changes, as a result of anaphylaxis, have been demonstrated in multiple veterinary clinical reports. In one study, one dog progressed to severe hepatic compromise following an insect sting.<sup>20</sup> Another case report revealed significant postmortem changes in the hepatic system, including portal vein, central vein, and sinusoidal congestion following dexamethasone administration in a dog.<sup>15</sup> And a recent study revealed expected antemortem changes in the liver and gallbladder in dogs with anaphylaxis. This study showed that an increase in activity of the hepatic enzyme, alanine transaminase (ALT), and an abnormal gallbladder wall (eg, thickened wall with a distinctive striated pattern) proved to be significant markers of anaphylaxis in dogs with hypersensitivity reactions.<sup>73</sup>

There is little published information on the effects of acute systemic anaphylaxis in cats and the few that exist report almost entirely subjective assessments and clinical signs rather than objective physiological variables.<sup>74-76</sup> It was originally thought that cats could not be sensitized to foreign antigens, since no reliable method was developed until the late 1960s.<sup>74</sup> A recent *in vivo* study was conducted and aimed to understand the pathophysiology of anaphylaxis in *Dirofilaria immitis*-sensitized cats.<sup>74</sup> This was achieved by investigating objective physiological and hematological measurements after an IV antigen challenge and by describing the major clinical signs associated with it.<sup>74</sup> The main physiological effects found in this experimental model included severe dyspnea and reduced blood oxygen saturation, expired carbon dioxide, and systolic blood pressure. The most common and reliable hematological change associated with severe clinical effects of *D. immitis* antigen challenge was increased HCT. The loss of intravascular fluid during acute systemic anaphylaxis could explain the rise in HCT seen in this study. Also, increased sympathetic tone due to acute hypoxemia in acute systemic anaphylaxis could result in splenic contraction. Since the feline spleen has a large capacity to store both red blood cells and platelets, splenic contraction results in the addition of large numbers of these cells to the circulating pool.<sup>74</sup> Sustained dyspnea and gastrointestinal signs were the most common clinical manifestations of anaphylaxis in the antigen-challenged cats. This *in vivo* study concluded that IV challenge with *D. immitis* antigen in sensitized cats resulted in dyspnea, hypoxemia, and systemic hypotension accompanied by hemoconcentration.<sup>74</sup> The rationale for this work was to provide a feline model of acute systemic anaphylaxis, presenting an objective framework for comparison with other species in which the lung is the main shock organ and the possible development of therapies for anaphylaxis.<sup>74</sup>

### **Etiology and Clinical Manifestations**

Virtually any agent capable of activating mast cells or basophils might potentially cause anaphylaxis.<sup>43</sup> The most common antigens identified in the veterinary literature include insect and reptile venom, antimicrobial agents, NSAIDs, opiates, vaccines, blood-based products, radio-contrast agents, food, and physical factors (ie, cold and exercise).<sup>15,57,70,82</sup>

Signs and symptoms can be divided into 4 major categories: cutaneous, respiratory, cardiovascular, and gastrointestinal. In people, the most frequent manifestations of anaphylaxis are cutaneous, occurring in 80–90% of reported series.<sup>56</sup> Cutaneous signs are considered as potential precursors to more severe anaphylactic reactions.<sup>4,56</sup> However, they may be delayed or absent in rapidly progressive anaphylaxis.<sup>1,27,56,73</sup> Severe episodes characterized by rapid cardiovascular collapse and shock can occur without cutaneous manifestations.<sup>1,4,27,56</sup> Cutaneous symptoms seen in dogs and cats commonly consist of generalized erythema, urticaria, pruritis, and facial angioedema.<sup>57,70</sup> Although cutaneous signs are commonly reported in anaphylaxis, these symptoms are often subtle and short-lived.<sup>2,57,83</sup> A recent study in canine hypersensitivity patients found that cutaneous manifestations were milder and more challenging to identify in patients with anaphylaxis, most likely because of their fur and pigmentation, with only 57% having detectable cutaneous manifestations.<sup>73</sup> Common respiratory manifestations consist of dyspnea, bronchospasm, stridor, tachypnea, and cough.<sup>57</sup> Dyspnea results from laryngeal and pharyngeal edema, bronchoconstriction, and excessive mucus production. The cardinal clinical feature of cardiovascular compromise during anaphylaxis is hypotension.<sup>84</sup> This may be associated with clinically obvious vasodilation (ie, generalized erythema) or a rapid onset of shock with peripheral circulatory failure. Clinical signs in dogs may include pale mucous membranes with a prolonged capillary refill time, poor pulse quality, hypothermia, and a depressed to dull mentation.<sup>70</sup> The main cardiovascular changes are fluid extravasation and vasodilation, causing a mixed distributive-hypovolemic shock pattern.<sup>84,85</sup> Increased vascular permeability, a key characteristic feature of anaphylaxis, allows massive fluid shifts of as much as 35% of the intravascular volume into the extravascular space within 10 minutes.<sup>1,2,27,33,56,84,85</sup> The redistribution of blood volume can result in rapid hemodynamic collapse, with little or no cutaneous or respiratory manifestations. Additionally, anaphylaxis is often associated with a compensatory tachycardia occurring in response to the decreased effective vascular volume.<sup>84,86</sup> However, bradycardia, presumably caused by increased vagal reactivity, can also occur.<sup>3,42,84,87</sup> Other cardiovas-

cular signs include arrhythmias, myocardial ischemia, and cardiac arrest.<sup>57,84</sup> Gastrointestinal symptoms are common but nonspecific, and include nausea, vomiting, and diarrhea, which may be hemorrhagic.<sup>4,28,56,57</sup> Other manifestations of anaphylaxis include neurologic and ocular signs, such as weakness, syncope, seizures, conjunctival injection, and lacrimation.<sup>57,70,71</sup>

Dogs usually exhibit signs related to the general systemic circulatory system. Hypotension and cardiovascular collapse are often clinically observed, while signs of respiratory compromise are less common.<sup>41,57,73</sup> In addition, hepatic signs are also predominant.<sup>57,73,80,88</sup> Hepatic venous congestion is manifested which results in portal hypertension and visceral pooling of blood leading to vomiting and diarrhea.<sup>57,59,73,88</sup> Immediate and fulminating hemorrhagic enteritis is one of the main antemortem clinical manifestations in dogs, while severe congestion of the liver and intestines is observed at necropsy.<sup>88–90</sup> Cats often exhibit pulmonary and gastrointestinal signs, with respiratory distress being typically the first sign observed.<sup>57,74–76</sup> Other manifestations observed in cats include hypersalivation, facial swelling, severe pruritis, incoordination, vomiting, and hemorrhagic diarrhea, which may eventually lead to hypovolemic shock.<sup>24,41,57,91</sup>

There appears to be a lack of reported anaphylactic reactions described in cats in the veterinary literature. It may be because these systemic reactions do not occur as frequently or simply go unrecognized compared to dogs. Three recent publications further support this. A retrospective study, evaluating the incidence of vaccine-associated adverse events (VAAEs), showed that the overall VAAE rate within 3 days of vaccine administration in cats was approximately 25% greater than in dogs.<sup>91,92</sup> Nonspecific systemic reactions with clinical signs of anorexia, lethargy, fever, or soreness were the most common VAAEs observed. However, clinical signs attributable to anaphylaxis (eg, vomiting, facial edema, and pruritis) were less common in this cat population than reported in dogs. Specific causes of vaccine-induced immediate-type hypersensitivity reactions have not been investigated in cats, but heterologous proteins (eg, bovine serum albumin) found in vaccines have been implicated as a cause in dogs.<sup>93</sup> Also, a published report describing an anaphylactic event due to ophthalmic medication in a cat might have helped increase public awareness. Two additional cases were reported to the pharmaceutical company shortly thereafter.<sup>18</sup> There is rising concern that many more cases of anaphylaxis due to ophthalmic medications have gone unrecognized and potentially attributing the cause of death related to the anesthesia rather than anaphylaxis during routine surgeries. Another recent publication showed similar

findings, where only half of the cases were reported to a regulatory agency or pharmaceutical company following anaphylactic reactions to ophthalmic antibiotics in cats.<sup>24</sup>

Anaphylaxis usually occurs rapidly, eliciting clinical signs within minutes of antigenic exposure (5–30 minutes), followed by rapid progression over minutes to hours.<sup>2,3,33,34,43,56,57</sup> Occasionally, some reactions may not develop for several hours. As a general rule, the onset of clinical signs is directly proportional to the severity of the systemic reaction; the sooner the syndrome manifests after antigenic exposure, the more severe the reaction will be.<sup>1,4,15,33,46,49,56,57,94</sup> An episode can abate and then exhibit a recurrence several hours after the disappearance of the original manifestations. Such events are termed “biphasic” anaphylactic episodes. The occurrence of biphasic reactions in the human literature appears to occur in as low as 1% to as high as 20% of anaphylactic reactions.<sup>1–3,42,43,87,95</sup> The reported time interval between the initial reaction and the onset of the second phase ranges from 1 to 72 hours (most within 8–10 hours).<sup>1–4,26,43,57,95</sup> Biphasic reactions, also referred to as late phase reactions, are thought to increase the risk of fatal anaphylaxis.<sup>1,43,56,95</sup> Persistent anaphylaxis, defined as an anaphylactic reaction that continues for a protracted period of time, has also been described in the human literature.<sup>2,4,43,55,96</sup> Although uncommon, some protracted reactions can last up to 32 hours, despite aggressive treatment.<sup>96</sup> Similar to biphasic anaphylaxis, it is impossible to anticipate these reactions based on initial clinical presentation.<sup>1,2,4,43</sup> Other types of hypersensitivity reactions can also occur days to weeks postantigenic exposure. These immune responses are known as type III or immune complex-mediated hypersensitivity reactions. Serum sickness is an example of this type of reaction.<sup>97–99</sup> The pathogenesis involves synthesis of antibodies (IgG) that bind to the antigens, forming soluble immune complexes in the presence of antigen excess. An inflammatory cascade ensues as complement is bound and anaphylatoxin is generated, leading to mast cell degranulation.<sup>100,101</sup> Histamine released from mast cell granules causes increased vascular permeability, local platelet aggregation, and vasoactive amine release from activated platelets.<sup>100</sup> The cascade of events leads to basement membrane damage with resultant vasculitic skin lesions, immune-mediated polyarthritis, proteinuria, and myocardial lesions, with potentially, secondary arrhythmias.<sup>102</sup> In people, signs can begin between 3 and 21 days postexposure with most occurring at 7–10 days.<sup>97,99</sup> A recent publication described the first reported case of antivenin-associated serum sickness in a dog.<sup>97</sup> Another report suggested that administration of human albumin solution in healthy dogs with normal serum albumin concentrations may result in signs of a

type III hypersensitivity. All dogs developed signs of a type III hypersensitivity reaction 5–13 days after administration of 25% human albumin solution. Clinical signs included lethargy, lameness, edema, and cutaneous lesions indicative of vasculitis, vomiting, and inappetence. All dogs included in the study were found to have anti-human albumin antibodies.<sup>102</sup>

Anaphylactic reactions after parenteral antigenic exposure are usually more immediate at onset, more rapidly progressive, and more severe in quality compared with those occurring after topical or cutaneous exposure.<sup>15,49,57</sup> It can be difficult to predict the rate of progression or the ultimate severity of the reaction since anaphylactic episodes can manifest in unusual ways. Anaphylaxis can also resolve spontaneously within minutes to hours if there is sufficient endogenous production of compensatory mediators, such as epinephrine, angiotensin II, and endothelin.<sup>30,42,53</sup> One study evaluating insect sting hypersensitivity reactions in humans showed gradual hemodynamic recovery over a period of 60–90 minutes postchallenge, and did not seem directly related to any specific therapeutic intervention.<sup>53</sup> However, in fatal cases of anaphylaxis, cardiovascular and respiratory disturbances predominate and usually occur early.<sup>15,33,43,56</sup> Death as a result of anaphylaxis can occur within minutes<sup>1,2,56,103,104</sup> and is frequently reported to occur in less than 1 hour.<sup>70,71,73,105–108</sup> Anaphylaxis occurs as part of a dynamic continuum; symptoms not appearing immediately life-threatening may progress quickly unless treated aggressively.

### Diagnosis

Due to the lack of accepted standard working definition and wide variability of clinical manifestations, anaphylaxis can be difficult to diagnose.<sup>1</sup> The diagnosis is based primarily on a detailed history and clinical findings.<sup>1,2,26,27,33</sup> Information regarding a previous history of hypersensitivity reactions, recent vaccinations, previous transfusions, exposure to new foods, medications, and insect bites or stings should be included in the history.<sup>26,56</sup> Diagnosis also depends on pattern recognition. It involves the sudden onset of characteristic signs and symptoms after exposure to a known or potential stimulus, the time elapsed between exposure and symptom onset, and the evolution of these manifestations over minutes to hours.<sup>1,2,51</sup>

The vast majority of patients presenting with a history consistent with anaphylaxis will have experienced an anaphylactic event. Nonetheless, it is important not to immediately assume this diagnosis. Several systemic conditions may present themselves with similar clinical signs. Severe asthma, pheochromocytoma, vasodepressor events (vasovagal), and systemic mastocytosis

should be considered in the differential diagnoses of anaphylaxis.<sup>4,56,57</sup> In addition, other causes of shock, cardiovascular and respiratory events of unknown etiology have the ability to mimic the clinical presentation of anaphylaxis.<sup>56</sup> IV lipid emulsion has also been reported to cause clinical “anaphylactoid-like signs,” which can occur within 20 minutes of administration.<sup>109</sup> These reactions are rare and have been reported to occur in less than 1% of human cases. Clinical signs include fever, nausea, vomiting, dyspnea, tachypnea, cyanosis, arrhythmias, hypotension, and cardiovascular collapse.<sup>110,111</sup> Adverse effects of IV lipid emulsion are due to direct reaction to the emulsion, which results in an acute adverse pyrogenic reaction or “colloid reaction.”<sup>111</sup>

### Clinical criteria

Universal clinical criteria for classifying anaphylaxis have recently been defined in people.<sup>1-3,27,56</sup> However, complete universal criteria have not been established for any other species. In 2005, an international panel, recruited by the National Institutes of Health (NIH) and the Food Allergy and Asthma Network (FAAN), delineated the clinical characteristics that would establish a diagnosis of anaphylaxis. This classification highlights a two-system involvement that makes anaphylaxis highly likely even though a known allergen had not been encountered, and a one-system event (eg, shock) if a known allergen had been encountered.<sup>1-3,27,56</sup> Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled: (1) the acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, and at least 1 of the following: (a) respiratory compromise; (b) or reduced blood pressure or symptoms of end-organ dysfunction; (2) 2 or more of the following that occur rapidly after exposure to a likely allergen for that patient—involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure, or associated symptoms of end-organ dysfunction and/or persistent gastrointestinal symptoms; or (3) reduced blood pressure after exposure to a known allergen (Table 1).<sup>1-3,27,56</sup>

Although no criteria will provide 100% sensitivity and specificity, it is believed that the criteria proposed should accurately identify anaphylactic reactions in more than 95% of cases.<sup>1,2</sup> Nevertheless, although these criteria proclaim to be useful, their utility and value in the human and small animal population require further investigation. Since their development, no further attempts have been made to establish diagnostic criteria.

### Biomarkers

There are more than 100 biomarkers for mast cell and basophil activation.<sup>51</sup> Clinical laboratory tests cur-

**Table 1:** Clinical criteria for diagnosing anaphylaxis<sup>1-3,27,56</sup>

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives; pruritus or flushing; swollen lips, tongue, vulva)  
And at least 1 of the following:
  - a. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
  - b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, collapse, syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a *likely* allergen (minutes to several hours):
  - a. Involvement of the skin/mucosal tissue (eg, generalized hives, pruritus, flushing)
  - b. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
  - c. Reduced BP or associated symptoms of end-organ dysfunction (eg, collapse, syncope, incontinence)
  - d. Persistent gastrointestinal symptoms (eg, abdominal pain, vomiting)
3. Reduced BP after exposure to a *known* allergen (minutes to several hours):
  - a. Infants and children: low systolic BP or > 30% decrease in systolic BP
  - b. Adults: systolic BP < 90 mm Hg or > 30% decrease from their baseline

rently available to support the diagnosis of anaphylaxis in people include histamine and total tryptase concentrations.<sup>1-4,31,33,46,47,51,87</sup> Their usefulness is limited by several factors. These biomarkers have sub-optimal sensitivities and specificities, assays are not universally available and generally are unable to be performed on an emergency basis.<sup>1,47,56,108</sup> Also, samples must be obtained in fairly close proximity to the reaction to be valuable.<sup>2-4,87</sup> Total tryptase measurement is currently the most widely used laboratory test to confirm a diagnosis of anaphylaxis in people.<sup>3,87</sup> The optimal time to obtain a serum tryptase is within 3 hours of the onset of symptoms.<sup>2,46,51,56</sup> Tryptase concentrations generally correlate with the clinical severity of anaphylaxis.<sup>31,33,47</sup> However, the route of allergen exposure appears to influence tryptase concentrations.<sup>33,47</sup> As a result, serum tryptase levels may correlate poorly to food triggered anaphylaxis.<sup>2,3,31,33,47,51</sup> Also, tryptase concentrations are rarely increased when hypotension or shock is absent.<sup>2,49,51</sup> Nonetheless, postmortem measurements of serum tryptase might be useful in establishing anaphylaxis as the cause of death in subjects experiencing sudden death of uncertain cause.<sup>2</sup> Generally, serial measurement of tryptase concentrations are reported to be more useful than measurement at only one point in time.<sup>2,47,51</sup> Plasma and urinary histamine are also commonly used as biomarkers. Plasma histamine concentrations typically peak within 5–10 minutes of onset of



the inciting trigger, and decline to baseline within 60 minutes.<sup>2,31,47,56</sup> Concentrations must, therefore, be measured within 1 hour of the onset of symptoms to obtain optimal results.<sup>2,3</sup> Increased plasma histamine concentrations correlate with anaphylaxis symptoms and are more likely to be increased than serum total tryptase concentrations.<sup>3,47</sup> However, due to its very short half-life in plasma (15–20 minutes), this test appears impractical in many clinical circumstances. Measurement of histamine or the histamine metabolite *N*-methylhistamine in a 24-hour urine collection may be more helpful.<sup>56</sup>

Serum tryptase and histamine concentrations as biomarkers have reasonably good specificity, but less than desirable sensitivity. Normal concentrations of either total tryptase or histamine do not rule out the clinical diagnosis of anaphylaxis.<sup>2,31,47</sup> Unfortunately, histamine and tryptase measurements are not readily available to veterinarians, their function has yet to be established in animals, and further studies are needed to determine their usefulness. Additional mast cell activation products have been recently investigated as potential confirmatory biomarkers of anaphylaxis in people. These include measurement of plasma or serum concentrations of mature  $\beta$  tryptase,<sup>108</sup> mast cell carboxypeptidase A3,<sup>2,47</sup> chymase,<sup>47</sup> PAF,<sup>112</sup> cytokines,<sup>112</sup> as well as urinary levels of LTE4.<sup>51</sup> Despite their promising results, they currently remain experimental. Given that different biomarkers are released at different times from activated mast cells and basophils during anaphylaxis, and patients present at different times after symptom onset; measurement of a panel of biomarkers may be more helpful than measurement of a single biomarker.<sup>47,51</sup>

Identification of biomarkers in veterinary patients would be particularly valuable since obtaining a pertinent history from pet owners can often be challenging. A recent study investigated hepatobiliary parameters (ie, ALT and gallbladder wall abnormalities as seen on ultrasound evaluation) in the canine hypersensitivity patient.<sup>73</sup> During anaphylaxis, alterations in blood flow and possible direct effects of inflammatory mediators causes injury to the hepatocyte.<sup>73,78,79</sup> ALT, a cytosolic hepatocellular enzyme, is found in abundance in these cells. The subsequent alterations to the hepatocytic membrane permeability result in excessive leakage of cytosolic enzymes. ALT is known to be a sensitive indicator of hepatic damage with a half-life of approximately 60 hours in the dog.<sup>73</sup> The results of the study showed that at the onset of an episode, ALT rapidly increases (<12 hours), peaks in 24–48 hours, and returns to normal over a period of 2–3 weeks.<sup>73,78,80</sup> Multiple striations in the gallbladder wall (eg, halo or double rim effect) are indicative of inflammation that can be related to causes independent of gallbladder disease. The reported changes

to the gallbladder wall (significant thickening and a distinctive striated pattern) in this study were almost immediate following an episode and were associated with impaired venous drainage as previously reported in canine anaphylaxis.<sup>71,73,78</sup> The reported sensitivities and specificities were 85% and 98%, respectively, for increased ALT, and 93% and 98%, respectively, for gallbladder wall abnormalities. This study concluded that the increase in ALT concentration and a thickened, striated gallbladder wall correlated significantly with anaphylactic reactions and were valuable biomarkers in supporting the diagnosis of canine anaphylaxis.<sup>73</sup> Although this study showed promising results, further investigations are needed in a larger population size to determine their practicality.

### Skin allergy testing

Various allergy testing, either by serological or via intradermal skin injections are available. Unfortunately, the association between the results of such tests and the risk of a reaction is poor. Various tests have either a low specificity or low sensitivity for the diagnosis or prediction of reactions.<sup>1</sup> Such testing is most accurate when performed after an anaphylactic event; it must be carried out within 4–6 weeks due to possible depletion of IgE, mast cell, or basophil levels, and may be of some use in documenting hypersensitivity to a particular trigger following a reaction.<sup>1</sup> However, even a positive result may not necessarily predict a future adverse reaction, since such results may be indicative merely of previous exposure and not necessarily hypersensitivity.<sup>47,51</sup> Therefore, skin tests and measurements of allergen-specific IgE may be useful in determining sensitization; however, they are not performed without risk and do not necessarily predict the severity of, or risk of fatality in a future anaphylaxis episode.<sup>1,31,42,83</sup>

Despite scientific efforts, the goal of developing rapid, sensitive, and specific laboratory tests to diagnose anaphylaxis remains elusive. Consequently, anaphylaxis remains a clinical diagnosis based on probability and pattern recognition, with laboratory tests being of little assistance in the immediate direction of patient treatment.

### Treatment

Anaphylaxis is a true medical emergency. There is considerable controversy about the choice of treatment for anaphylactic reactions with therapy appearing to be mostly symptom-based. Most recommendations are based solely on subjective clinical experience and opinion.<sup>2</sup> Prompt assessment and management are critically important. The fundamentals of basic life support form the mainstay of the initial management of

anaphylaxis; treatment begins with a rapid assessment of airway, breathing, circulation, and mental status. Aggressive treatment should be initiated before diagnostics are performed since rapid and progressive deterioration and mortality can occur frequently. In Hymenoptera stings in dogs, severe systemic anaphylactic signs usually are apparent within 15 minutes of the bee or wasp sting and can rapidly lead to death if left untreated.<sup>106</sup> A recent retrospective study reported that the majority of anaphylactic reactions occurred within 5 minutes of ophthalmic antibiotic application in cats, with some reactions being observed within the first 60 seconds of allergen exposure.<sup>24</sup> Consequently, delay in treatment leads to an increased likelihood of poor outcome with potential life-threatening consequences.<sup>2,73,113</sup> No randomized controlled trials that meet optimal standards have been published for any medication used in the treatment of acute anaphylaxis; however, strong evidence base for epinephrine supports its use as a first line drug.<sup>1,2,4,26,51,56,94,114,115</sup>

### Epinephrine

Epinephrine is a natural body constituent, comprising approximately 80% of the catecholamines in the adrenal medulla.<sup>115</sup> During life-threatening situations, endogenous epinephrine is released and impacts innervated structures throughout the body. This, in turn, accelerates the heart rate and consequently increases the force of cardiac contractions. While blood pressure rises, blood flow is redistributed from the skin and SC tissue to the skeletal muscles, splanchnic circulation, and brain. Oxygenation tends to increase, blood glucose rises, and the body is prepared for a state of "fight or flight."<sup>115,116</sup> Currently, the World Health Organization (WHO) and the WAO consider epinephrine to be an essential medication for treatment of anaphylaxis.<sup>2</sup>

### Pharmacology effects of epinephrine

Relative to anaphylaxis, its most important effects occur in the cardiovascular system and the vascular smooth muscle.<sup>117</sup> Epinephrine stimulates both  $\alpha$  and  $\beta$  adrenergic receptors. Epinephrine's  $\alpha_1$ -adrenergic effects result in vasoconstriction, leading to increases in peripheral vascular resistance, blood pressure, and coronary artery perfusion, as well as decreases in mucosal edema within the airways.<sup>115,117</sup> Through its vasoconstrictor properties, it prevents and relieves upper airway obstruction and helps to prevent and relieve shock.<sup>94,115</sup> Its  $\beta_1$ -adrenergic effects include positive inotropic and chronotropic activity leading to an increase in CO.<sup>2,94,115</sup> The  $\beta_2$ -adrenergic effects of epinephrine result in bronchodilation, suppressed release of mediators of inflam-

mation from mast cells and basophils, and relief of urticaria.<sup>2,115,117</sup> Regardless of the route of administration, epinephrine has a short duration of action and a narrow therapeutic index.<sup>94,115</sup> It also has biphasic pharmacologic effects. A low dose of epinephrine might have the opposite effect of which it is intended and might lead to vasodilation and increased release of mediators of inflammation.<sup>115</sup>

Despite epinephrine's multiple beneficial pharmacologic properties, serious adverse effects, such as ventricular arrhythmias, hypertensive crisis, myocardial infarction, and pulmonary edema, have been reported, especially after an overdose of epinephrine by any route of administration (most commonly following an IV bolus injection).<sup>115</sup> Usually mild and transient pharmacologic effects, such as pallor, tremor, anxiety, palpitations, and dizziness, are expected and occur within minutes after epinephrine injection.<sup>2,115,118,119</sup> However, concerns about the potential serious adverse effects of epinephrine need to be weighed against concerns about the cardiac manifestations of untreated anaphylaxis.<sup>2,114,115,118,119</sup>

### Clinical relevance of epinephrine

Epinephrine's efficacy has been evaluated through in vitro and vivo studies. Conflicting conclusions have been deduced from these studies. In vitro studies concluded that epinephrine is beneficial when administered prior to allergen challenge. The  $\beta$ -adrenergic effects of epinephrine cause an increase in intracellular 3'5'cAMP, which, in turn, inhibits mediator release during immunologic challenge.<sup>57,120,121</sup> This finding supports the rationale for its use. Although, in vivo studies, conducted to date, showed that epinephrine was of little or no benefit when administered during fully developed shock.<sup>120-122</sup> A canine ragweed model was used to examine the effect of IV bolus epinephrine on improving systemic hemodynamics in anaphylactic shock.<sup>120</sup> When epinephrine (at 2 different doses: 0.01 mg/kg and 0.025 mg/kg IV) was given during maximal hypotension, only transient increases in mean arterial pressure (MAP), CO and pulmonary wedge pressure (Pwp) were observed. By 20 minutes postshock, these values were not different from control values. This study concluded that no positive effects were observed on reversing cardiovascular collapse when an IV bolus of epinephrine was administered during maximal hypotension. In fact, deleterious effects on cardiac mechanics and mediator release were found when a higher bolus dose of epinephrine was used.<sup>120</sup> Another study showed similar findings, where no beneficial effect of epinephrine was observed after fully developed shock to Hymenoptera venom allergen in people.<sup>53</sup>

### Administration routes

The various proposed routes of epinephrine administration include IV, IM, or SC bolus injections, continuous IV infusion, and inhalation from a metered-dose inhaler. The route of administration and dose in anaphylaxis remain empiric and controversial. The SC route should be avoided for multiple reasons.<sup>1,2,57,115,121,122</sup> The powerful vasoconstrictor effect of epinephrine injected into SC tissue potentially delays absorption and consequently, the onset of pharmacologic effects. In addition, low tissue concentration of epinephrine concentrations can lead to increased vasodilation and increased mediator release.<sup>115</sup> Also, SC administration route is more likely to cause unpredictable results.<sup>121</sup>

Continuous IV infusion has been shown to be the preferred route in the treatment of anaphylaxis in dogs.<sup>57,121</sup> An anesthetized ragweed-sensitized dog model was used to further support this.<sup>121</sup> When administered at the initiation of an allergen challenge, bolus treatment of epinephrine, at a dose of 0.01 mg/kg, by IM, IV, or SC routes, respectively, caused limited measurable beneficial effects. In contrast, constant infusion of epinephrine at a lower total dose (mean value of approximately 0.05 µg/min/kg) produced significant hemodynamic improvement.<sup>121</sup> The results showed that MAP, CO, stroke volume, and cardiac stroke work (SW) measured in the constant infusion study were significantly greater than values obtained in bolus studies.<sup>120</sup> In the constant infusion study, CO remained higher for up to 90 minutes postshock, while MAP remained higher for 20–30 minutes postshock, stroke volume for 20–40 minutes postshock, and SW for up to 90 minutes postshock. The improvement in MAP noted in the continuous infusion study appeared to be because of epinephrine's β-effect on the heart, and not to its α1-vasoconstrictive effect on the systemic vasculature.<sup>121</sup> Another study compared the effects of bolus IV, SC, and IM epinephrine on hemodynamic recovery in fully developed canine anaphylaxis and found that although higher epinephrine concentrations were observed in the IM and IV studies, no difference among the 3 bolus treatment studies as compared with a nontreatment study was observed once mediators have already been released.<sup>122</sup>

Epinephrine is the treatment of choice and the first drug administered for anaphylaxis, as confirmed internationally by most consensus anaphylaxis guidelines.<sup>1,2</sup> Rapid achievement of peak plasma and tissue epinephrine levels appears to optimize survival, as human and animal studies demonstrate that delayed administration is associated with poor outcomes.<sup>1,2,51,53,94,117,120–122</sup> Therapeutic recommendations for epinephrine use in

anaphylaxis are largely based on clinical pharmacology studies, clinical observation, and animal models.<sup>94</sup>

### Clinical recommendations

Epinephrine at a dose of 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution via IM route (maximum dose of 0.3 mg in patients < 40 kg and 0.5 mg in patients > 40 kg) is recommended for the initial treatment of anaphylaxis.<sup>1,2,57,70,94</sup> Depending on the severity of the episode and the response to the initial injection, the dose can be repeated every 5–15 minutes, as needed. However, if shock has already developed, epinephrine should be given by slow IV infusion (0.05 µg/kg/min), ideally with the dose titrated to clinical response.<sup>57,121</sup> The SC route should be avoided.<sup>1,2,57,115,121</sup>

Currently, the optimal way of providing first-aid treatment in people with anaphylaxis outside of the hospital setting is through an IM epinephrine auto-injector (EpiPen<sup>a</sup>).<sup>123</sup> Although they are not routinely prescribed in veterinary medicine for a variety of reasons, their usefulness may be beneficial in patients with a history of an anaphylactic episode. Their effectiveness has not been investigated in veterinary patients. Epinephrine auto-injectors are currently available in 2 fixed doses only: 0.15 and 0.3 mg.<sup>1,2,27,123</sup> It would, therefore, be difficult to dose patients weighing less than 15 kg accurately. Additional fixed doses would be needed for smaller patients. Also, the auto-injectors available have a relatively short needle length (ranges between 1.27 and 1.58 cm).<sup>115,124</sup> On the basis of a patient's body mass index, the needle might not be long enough to reach IM tissue in some patients (especially in overweight or obese patients).<sup>124</sup> In addition, most epinephrine auto-injectors available have a relatively short shelf-life of only 12–18 months.<sup>123</sup> An alternative option to consider in veterinary patients may be providing pet caretakers with a prefilled epinephrine syringe for patients at risk of anaphylaxis recurrence. This would allow practitioners to provide adequate epinephrine dosing and accurate needle length customized to the patient needs. However, one major disadvantage is the short shelf-life (only 3–4 months) of the prefilled syringe.<sup>123</sup>

### Ancillary Treatments

Most of the guidelines proposed for the treatment of anaphylaxis are subjective and, therefore, should be individualized on a case-by-case basis. Treatment should be tailored to the type and severity of clinical signs. Indicated supportive care treatments include: antihistamines, glucocorticoids, bronchodilators, oxygen, and fluid therapy.

## Antihistamines

Histamine concentrations peak at the onset of anaphylaxis and return rapidly to normal, despite severe hemodynamic compromise. Pretreatment with antihistamines is widely practiced; however, there is little evidence supporting their usefulness in preventing an anaphylactic response.<sup>5,125,126</sup> Guinea pig studies have shown that although antihistamine pretreatment may ameliorate some early changes, they have little effect after the first 10 minutes.<sup>84,127</sup> In a canine model, treatment with antihistamines seemed to be ineffective in the treatment of anaphylaxis.<sup>126</sup> In a rat model, pretreatment with H1-antihistamines with or without concurrent H2-antihistamines worsened hypotension and decreased survival time.<sup>128</sup>

### H1-antihistamines

In an attempt to downregulate the allergic response and minimize the clinical impact of histamine release, H1-antihistamines are often given. These medications act as inverse agonists, and not competitive antagonists as previously described.<sup>2,59,125,129,130</sup> H1-antihistamines have a superior affinity for the inactive state of H1R. They stabilize the receptors in this conformation, and consequently shift the equilibrium toward the inactive state.<sup>59,125,129,130</sup> H1-antihistamines are effective in localized and less severe systemic allergic reactions.<sup>125</sup> In allergic rhinitis, H1-antihistamines relieve sneezing, itching, and rhinorrhea; in allergic conjunctivitis, they relieve erythema, itching, and lacrimation, whereas in urticaria, they relieve itching and whealing.<sup>125,129</sup> Due to deleterious inflammatory mediators (other than histamine) being released in more severe systemic responses, these reactions seem to respond poorly to a single mediator antagonist.<sup>125</sup> Although H1-antihistamines are expected to relieve cutaneous and nasal symptoms in anaphylaxis, they are neither expected to prevent or relieve the more serious clinical signs and symptoms, such as upper airway obstruction, gastrointestinal symptoms, or shock, nor do they prevent ongoing mediator release from mast cells and basophils.<sup>1,2,26,42,57,125,127,129</sup> A Cochrane systematic review found no high-quality evidence for or against the use of H1-antihistamines in treatment of anaphylaxis.<sup>125</sup> Recommendations for the use of H1-antihistamines have been outlined in numerous anaphylaxis guidelines.<sup>1,2,27,56,104</sup> However, this recommendation has been included into guidelines without a demonstrated effect ever being confirmed.<sup>125,130</sup> There might be no advantage for the use of H1-antihistamines or the adverse effects might actually be worse than the effect itself.<sup>125</sup>

There are two main functional classes of H1-antihistamines in veterinary medicine: first- and second-

generation H1-antihistamines. First-generation compounds commonly used in veterinary medicine include diphenhydramine, chlorpheniramine, cyproheptadine, and hydroxyzine. First-generation H1-antihistamines have more unfavorable side effects.<sup>59,125,129–131</sup> They cross the blood-brain barrier and in usual doses may cause CNS depression (eg, drowsiness, somnolence, and cognitive function impairment) and gastrointestinal signs, such as vomiting, diarrhea, and anorexia. Overdosage may even cause death in some cases.<sup>125</sup> Although second-generation H1-antihistamines have not shown greater efficacy over the first generation compounds in veterinary patients with allergic disorders, they are relatively safer.<sup>59</sup> However, second-generation H1-antihistamines are not available for parenteral use. Examples of second-generation compounds include loratadine, fexofenadine, and cetirizine.

### H2-antihistamines

H2-antihistamines, similar to H1-antihistamines, are inverse agonists. Treatment with a combination of H1- and H2-antihistamines has been reported to be more effective in attenuating the cutaneous manifestations of anaphylaxis than treatment with H1-antihistamines alone.<sup>129,131</sup> Nonetheless, H2-antihistamines are recommended in only a few current anaphylaxis guidelines.<sup>1,2,27,29,56,96</sup> Ranitidine and cimetidine have been most studied, but no controlled studies have demonstrated superiority of one H2-antihistamines over another.<sup>1</sup> H2-antihistamines have low potential to be harmful; however, cimetidine can lead to hypotension if infused rapidly.<sup>1,2,26,56,130</sup> Although H2-antihistamines have been studied in anaphylaxis, limited evidence supports their role in treatment of this syndrome.<sup>2,131,132</sup>

In a canine ragweed model of anaphylaxis, pretreatment with H1R, H2R, and H3R antagonists was examined, and their usefulness was evaluated in preventing the depression in left ventricular (LV) contractility as expected to occur in anaphylaxis.<sup>62</sup> The drug studies included an H1R antagonist study in which chlorpheniramine maleate (10 mg/kg IV) was infused prior to challenge, an H2R antagonist study, in which ranitidine hydrochloride (20 mg/kg IV) was administered, and an experimental H3R antagonist study in which thioperamide maleate (1 mg/kg IV) was given. The results concluded that only H3R antagonist showed positive results. H3R antagonist was associated with higher heart rates and cardiac SW as compared with H1R and H2R antagonist treatment studies.<sup>62</sup>

Overall, antihistamines should never be substituted for epinephrine in the treatment of anaphylaxis. However, administered as an ancillary treatment, alone or in combination, antihistamines may relieve cutaneous

signs and symptoms (especially urticaria and pruritis) as well as decrease gastric acid secretion.<sup>1,2,4,27,29,56,57,129,131</sup>

#### Clinical recommendations

Diphenhydramine, an H1-antihistamine may be given IM or PO at a dosage of 1–4 mg/kg in dogs<sup>59,133</sup> and 0.5–2 mg/kg IM or PO in cats,<sup>133</sup> every 8–12 hours. Diphenhydramine can also be given IV slowly at a dosage of 0.5–1 mg/kg in dogs (without exceeding 50 mg total).<sup>57,70,133</sup> Ranitidine, an H2-antihistamine can be considered at a dose of 0.5–2.5 mg/kg IV, PO, or SC.<sup>57,133</sup> If given intravenously, it should be infused slowly over a period of 10 minutes, as rapid administration may cause the development of transient cardiac arrhythmias. It may also be diluted in 5% dextrose in water (D5W) to a volume of 20 mL and injected over 5 minutes.<sup>4,43</sup>

#### Glucocorticoids

Glucocorticoids continue to be frequently used in the treatment for anaphylaxis. Their usefulness in other allergic diseases has led to their incorporation into anaphylaxis management.<sup>1</sup> Their administration usually consists of either a single dose or a dose on the day of the event followed by a dose on each of the next few days.<sup>134</sup> Although short-term glucocorticoid treatment is rarely associated with adverse effects,<sup>2,134,135</sup> this class of drug does not relieve the initial symptoms and signs of anaphylaxis and, therefore, should never be used as a first-line drug.<sup>1,2,134</sup> The onset of glucocorticoids' beneficial effects takes several hours (at least 4–6 hours), regardless of the route of administration.<sup>2,130</sup> The primary mechanism of action of this drug in anaphylaxis is downregulation of the late-phase eosinophilic inflammatory response, as opposed to the early phase response. It switches off transcription of a multitude of activated genes that encode proinflammatory proteins.<sup>2,130,134</sup> Glucocorticoids also block the arachidonic acid cascade and may relieve protracted symptoms and prevent biphasic anaphylaxis, although there is no evidence to prove this.<sup>1,2,26,56,57,95,130,134</sup> Nevertheless, despite their current common use, a Cochrane systematic review found no relevant evidence for the use of glucocorticoids in the treatment of an acute episode of anaphylaxis.<sup>134</sup> Also, several glucocorticoid drugs are among the most commonly reported triggers of anaphylaxis in people.<sup>1,2</sup> Although this occurrence is rare in veterinary patients, the first case describing a fatal case of anaphylaxis in a dog associated to a routine dexamethasone suppression test was recently reported.<sup>15</sup> A common misconception among practitioners is the belief that pretreatment with corticosteroids and antihistamines will prevent anaphylaxis from occurring. On the contrary, pretreatment will

not prevent a reaction, but simply may blunt the physiologic response.

#### Clinical recommendations

Dexamethasone sodium phosphate can be administered at a dosage of 1–4 mg/kg IV,<sup>70</sup> methylprednisolone sodium succinate at a dosage of 30 mg/kg IV,<sup>57</sup> or prednisone sodium succinate at a dosage of 10–25 mg/kg IV.<sup>70</sup> Oral administration of prednisone, 0.5–1.0 mg/kg, might be sufficient for milder attacks.<sup>1</sup>

#### Bronchodilators

Selective  $\beta_2$ -adrenergic agonists, such as albuterol (salbutamol), may be beneficial in anaphylaxis as an adjunctive therapy for treatment of respiratory signs.<sup>1,2,26,27</sup> It is usually given by the inhaled route for direct effect on bronchial smooth muscle, for the relief of bronchospasm. Although this class of drug is helpful for lower respiratory tract symptoms, it should not replace epinephrine since it has minimal  $\alpha_1$ -adrenergic agonist vasoconstrictor effects and does not prevent or relieve laryngeal edema or upper airway obstruction.<sup>1,2,5,40</sup> Potential adverse effects include tremors and tachycardia. Overdose of this drug may result in hypokalemia and vasodilation.<sup>4</sup> In addition, aminophylline, a phosphodiesterase inhibitor bronchodilator, may also be beneficial in the treatment of systemic anaphylaxis. It is believed that aminophylline competitively inhibits phosphodiesterase thereby increasing amounts of cAMP, which in turn increases the release of endogenous epinephrine. The elevated levels of cAMP may also inhibit the release of histamine and SRS-A. Moreover, it directly relaxes smooth muscles in the bronchi and pulmonary vasculature.<sup>133</sup>

#### Clinical recommendations

The recommended dose of albuterol is 0.5 mL of 0.5% solution in 4 mL of isotonic saline by nebulizer every 6 hours or 90  $\mu$ g/actuation (1–2 puffs) by metered-dose inhaler every 15 minutes, up to 3 doses.<sup>4,57,133</sup> Aminophylline is recommended at a dose range of 5–10 mg/kg IM or slowly IV.<sup>70,133</sup>

#### Fluid resuscitation

Aggressive fluid resuscitation is recommended for hypotensive patients. Rapid IV infusion of isotonic crystalloid (ie, normal saline or lactated Ringer's solution) should be administered as soon as the need is recognized. Within a few minutes of a severe reaction, a significant portion of the blood volume extravasates. Combined with vasodilatory pooling, the reduction in the

effective circulating blood volume leads to distributive shock.<sup>1,85</sup> Thus, IV fluids are critical to prevent cardiovascular collapse. Resuscitative volumes of crystalloids (90 mL/kg dog and 60 mL/kg cat)<sup>57,70</sup> should be given rapidly at the onset of an anaphylactic reaction. Colloid support (eg, dextrans or hetastarch) may be beneficial, as it provides a more rapid and prolonged hemodynamic response. Hetastarch can be administered at a dose of 5 mL/kg as an IV bolus over 15 minutes and can be repeated as needed up to a total daily dosage of 20 mL/kg.<sup>70</sup> The fluid volume replaced should be titrated to the clinical response. Suggested parameters for optimal small animal fluid resuscitation are a central venous pressure of 5–10 mm Hg, systolic BP of 100–120 mm Hg, urine production of 0.5–1.5 mL/kg/h, PCV > 25%, lactate concentration < 2.5 mmol/L, improved mentation, and normothermia.<sup>136</sup> In a small percentage of cases, bradycardia may be the first clinical sign observed; this is a result of the Bezold-Jarisch cardiac reflex and is a response to sudden, dramatic hypovolemia caused by fluid extravasation. The slowing of the heart is likely a protective response to allow the ventricles to fill during severe volume deficit, and rapid volume expansion, rather than anticholinergic administration is therefore the most appropriate management.<sup>3,5,42,84</sup>

### Oxygen

High-flow oxygen (via a face mask, nasal cannulas, oxygen cage, or endotracheal tube) should be administered to all patients experiencing respiratory symptoms or hypoxemia. Those who are hemodynamically unstable may benefit from oxygen supplementation as well.<sup>57</sup>

### Treatment of Refractory Anaphylaxis

#### Vasopressors

Potent vasopressors, such as dopamine, norepinephrine, or vasopressin, may be required to overcome vasodilation if epinephrine and fluid resuscitation fail to maintain adequate systolic blood pressure. Dopamine (2.5–10 mg/kg/min) is a precursor of norepinephrine and exerts its effect in a dose-dependent manner: higher doses (5–10 mg/kg/min) result in increased myocardial contractility and vasoconstriction via stimulation of  $\beta_1$ - and  $\alpha_1$ -adrenoreceptors. Norepinephrine (0.01–1 mg/kg/min) causes vasoconstriction and a resultant increase in peripheral vascular resistance via potent  $\alpha_1$ - and  $\alpha_2$ -adrenoreceptor effects.<sup>137</sup> The effect of vasopressin on systemic anaphylaxis has not been investigated in animal models, although it has been described in human clinical case reports and experimental studies.<sup>138,139</sup> Two recent cases were reported in the human literature where anaphylactic shock was

successfully treated with arginine-vasopressin (AVP).<sup>138</sup> An experimental study, simulating the consequences of systemic anaphylaxis, investigated the effects of epinephrine, vasopressin, and inhibitors of NO and prostanoid pathways on histamine-induced relaxation in the human internal mammary artery.<sup>139</sup> They concluded that epinephrine was only partially effective in reversing histamine-induced vascular relaxation, whereas both vasopressin and methylene blue were able to completely reverse histamine-induced vasodilation.<sup>139</sup> Blockade of the target enzyme of NO pathway, guanylate cyclase, with vasopressin or use of methylene blue, may represent hopeful therapeutic options in the treatment of anaphylactic shock in animals in the near future.

The mechanism of action for AVP in vasodilatory shock is most likely secondary to its ability to block ATP-sensitive potassium channels ( $K_{ATP}$ ) in vascular smooth muscle and interfere with NO signaling.<sup>137</sup> A recent case series of dopamine resistant hypotension and vasodilatory shock in dogs revealed an increase in MAP within the first 15 minutes of exogenous AVP constant rate infusion therapy (0.5–1.25 mU/kg/min).<sup>140</sup> AVP acts as a potent vasoconstrictor by stimulation of V1 receptors in vascular smooth muscle, and should therefore be considered in small animal veterinary patients with vasodilatory shock that is unresponsive to fluid resuscitation and catecholamine administration.<sup>137,140</sup>

#### Glucagon and anticholinergic agents

Glucagon is a polypeptide with inotropic and chronotropic cardiac effects, independent of catecholamine. It may be useful in anaphylactic patients receiving a  $\beta$ -adrenergic blocker who fail to respond to epinephrine administration.<sup>1,2,56</sup>  $\beta$ -blockers may interfere with epinephrine treatment by antagonizing its effects at the  $\beta$ -adrenergic receptor.<sup>4,43</sup> Glucagon may reverse refractory bronchospasm and hypotension during anaphylaxis by activating adenylyl cyclase directly and bypassing the  $\beta$ -adrenergic receptor.<sup>141</sup> However, the occurrence and importance of this mechanism of action in anaphylaxis is unproven. The recommended dosage in people is 1–2 mg administered IV followed by an IV constant rate infusion of 5–15 mg/min titrated to clinical response.<sup>1,4,57</sup> Protection of the airway is important since glucagon may cause emesis and risk aspiration in severely sedated or obtunded patients.

Anticholinergic agents are also sometimes needed for patients on  $\beta$ -blockers. Atropine (0.02–0.04 mg/kg IV) may be indicated in those with persistent bradycardia and ipratropium (via inhalation; 18  $\mu$ g/actuation) in those with epinephrine-resistant bronchospasm.<sup>1,2,26,56,57</sup>

## Monitoring

After the treatment of an anaphylactic reaction and apparent resolution of symptoms, an observation period should be considered for all patients due to the risk of a biphasic reaction. Ideally, these patients should be closely monitored in a medically supervised setting for a period of 3 days, since these reactions can recur at any time during this period. Generally, the same organ systems are involved in the initial and secondary reaction and patients can progress from being relatively stable to a state of extremis in a very short time.<sup>4</sup> A case describing a biphasic reaction was recently reported in a dog with anaphylaxis following massive bee envenomation.<sup>19</sup> The dog initially presented with clinical signs of respiratory distress. After initial hemodynamic stabilization, the patient recovered well and was discharged from the hospital. Over a 48-hour period after the initial incident, the dog developed progressive tachypnea, vomiting, restlessness, and the subsequent development of acute respiratory distress syndrome (ARDS).

## Prognosis

The prognosis for anaphylaxis is individualized on the basis of the severity and the progression of the reaction. Airway signs will be more severe in patients with preexisting airway diseases, including those with an allergic component, such as asthma. However, there is no evidence that such patients are more likely to suffer an anaphylactic reaction. Dogs frequently present with a history of food allergies, including evidence of hypersensitivity to soy proteins.<sup>142</sup> However, whether hypersensitivity to dietary soy increases the risk of a reaction to soy lecithin found in propofol formulations is unknown. In people, documented egg allergy is not thought to increase the risk of a reaction to propofol, despite soylecithin formulations containing purified egg protein.<sup>143</sup>

Preventative measures rather than predictive testing are most likely to be useful in a patient with a history of a previous reaction. Most recommendations for preventing recurrences of anaphylaxis are simply strict avoidance of the specific trigger(s). Thus, obtaining a thorough and detailed history from pet caretakers following an episode is essential. As soon as the clinical diagnosis of anaphylaxis is suspected, discontinuing exposure to the trigger, if possible, is crucial. In addition, further educating clinicians and hospital staff personnel are needed to increase awareness of this severe reaction.

## Conclusion

Anaphylaxis is an acute, life-threatening systemic reaction with varied mechanisms, clinical presentations, and

severity that results from the sudden systemic release of mediators from mast cells and basophils. These catastrophic reactions represent true medical emergencies. In the past 100 years, great strides have been made in the understanding of the immunology and pathophysiology of anaphylaxis. Despite the impressive progress made in the management of this reaction, the investigation of anaphylaxis continues to be impeded by the lack of universally accepted definition and the absence of reliable laboratory biomarkers. This in turn has thwarted efforts to ascertain the incidence and outcome of anaphylaxis in our patients, to determine the most effective forms of therapy, and to identify patients at risk for life-threatening anaphylaxis. In addition, the variable clinical nature of the anaphylactic response indicates that there is still much we do not understand. It remains to be answered why some patients only have mild reactions, whereas others suddenly develop fatal reactions, and why some animals recover spontaneously, whereas others die despite rapid and heroic measures. Further studies are needed to elucidate the molecular, immunologic, and physiologic mechanisms responsible for anaphylaxis in order to evaluate more effective means of therapy. Moreover, further studies are warranted in establishing the appropriate dosing of the medications used in anaphylaxis and the role of other therapeutic interventions in order to guide optimal clinical decision making.

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## Footnote

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